20. ~~29~~. (New) The ischemia-damage mitigating compound or salt thereof of claim ~~28~~ 19 wherein R and R_1 are both not hydrogens and are meta to each other and to the heteroatom.

30. (New) The ischemia-damage mitigating compound or salt thereof of claim 28 wherein at least one of R and R_1 is COOH.

21. ~~31~~. (New) A pharmaceutical composition comprising a compound or salt thereof of claim ~~28~~ 19 in a pharmaceutically acceptable carrier.

22. ~~32~~. (New) A method of inhibiting tissue damage caused by ischemia, comprising administering an effective amount of a compound or salt thereof of claim ~~28~~ 19.--

REMARKS

Claims 1, 2 and 5-21 are pending, and claims 2 and 8-21 are allowed, while claims 1 and 5-7 stand rejected. By the present amendment, Applicants have cancelled claim 2 and added additional claims 28-32, leaving claims 1, 5-21 and 28-32 pending. For the record, Applicants note that Amendment B, filed September 5, 2000, was refused entry in the parent case, in the Advisory Action of September 20, 2000; and Applicants have not requested and do not wish to have that Amendment B entered in the present case. Therefore, prior to the present amendment, the pending claims remained as after entry of Amendment A of January 10, 2000.

Applicants have amended the claims to point out more clearly that which they consider to be their invention and to correct clerical errors. In particular, the misspelling of the term "pyridinium", which was incorrectly spelled "pyrdinium" (without the first "i"), has been corrected throughout all pending claims and the specification. In addition, Applicants have amended claim 7 to correct a clerical error, whereby the structural name for a preferred embodiment designated "AP5" was inadvertently omitted from the claimed list of compounds. This omission resulted in claim 7 reciting "1-phenacyl-2,5-dicarboxypyrdinium bromide (AP5)"

which incorrectly appeared to indicate that the structure of AP5 is "1-phenacyl-2,5-dicarboxypyrdinium bromide". In fact, the structure of AP5 is "1-phenacyl-3,5-dicarboxypyridinium bromide" (i.e., essentially the same as the compound recited immediately before "AP5" but including a *3*,5-dicarboxypyridinium moiety instead of a *2*,5-dicarboxypyridinium moiety). Claim 7 has been amended by inserting the above structural name for AP5 immediately before the recitation of "AP5". Applicants have similarly amended claims 14 and 21 to correct this same error of omission. Support for this amendment to correct the recitation of this preferred embodiment is provided in the specification, for instance at page 5, line 31 ("Preferably, R and R_1 are meta to each other and to the heteroatom.") and page 5, lines 31-32 ("Preferably, R is COOH. Preferably, R_1 is COOH.").

In addition, Applicants have amended the specification in like manner to correct this same error of omission, at page 5, line 36, by inserting the structural name "1-phenacyl-3,5-dicarboxypyridinium bromide" before the recitation of "AP5". Similarly, at page 36, line 4, Applicants have corrected an alternate structural nomenclature for the preferred AP5 embodiment, that also incorrectly recited a 2,5 configuration instead of the meta, 3,5 form, namely, "N-(2-phenacyl-2-oxoethyl)-2,5-dicarboxypyridinium bromide". This incorrect name was replaced with the corresponding correct 3,5 nomenclature, "N-(2-phenacyl-2-oxoethyl)-3,5-dicarboxypyridinium bromide".

Applicants note that, in the previous Advisory Action, similar claim amendments proposed in unentered Amendment B, to insert correct structural nomenclature for AP5, were not entered as they were said to raise new issues, including new matter. More particularly, the Advisory Action stated that "the amendment is not consistent between insertion and deletions." Applicants note that, in unentered Amendment B, only claims 14 and 21 were amended to insert the structure of AP5, whereas here the specification and all claims reciting the preferred AP5

embodiment have been amended consistently to recite correct structural nomenclature for this compound throughout the entire application.

Claims 28-32 have been added to describe additional embodiments of the invention which were provided in the original claims as filed. Thus, claim 28 corresponds to original claim 1, amended to recite a salt of the compound as well as a compound *per se*, with the addition of two provisos. Dependent claims 29-32 correspond, respectively, to original claims 2, 3 and 4 combined, 7 and 15 (with claims 31 and 32 further differing from original claims 7 and 15 in being dependent on claim 28 rather than being independent).

The claims have been further amended for clarification, as discussed below. Since no new matter is believed to be introduced, entry of this amendment and reconsideration of all pending claims are respectfully requested.

Claims 1, 6 and 7 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 1 is said to be indefinite because it does not recite the presence of an anion which the Examiner believes to be necessary. In particular, the Examiner notes that all of the examples are salts and therefore the claimed compound should be recited as a salt. Applicants have amended claim 1, and for consistency, all other previously pending claims (claims 5-21) to recite a salt of a compound of formula I.

Claim 1 is considered indefinite for reciting "either R or R_1 is COOH". The Examiner notes that this language appears to preclude the compound in which R and R_1 are both COOH. Applicants have amended claim 1 to expressly recite the compound in which R and R_1 are both COOH, by specifying that "at least one of R and R_1 is COOH". This phrase encompasses the previously recited feature, that "both R and R_1 cannot be hydrogen", which has therefore been deleted. Independent claims 8 and 15 have also been similarly amended.

Claims 1 and 5 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Gubin. The Examiner maintains that the claimed acid would have been obvious over the prior art disclosure of an ester. Applicants respectfully maintain that claim 1 as written prior to the present amendment would not have been obvious over the prior art. However, to expedite allowance of the present case, Applicants have amended claim 1 to incorporate the features of claim 2 which is indicated to be free of the prior art. Applicants therefore believe that claim 1 as presently amended is free of the present rejection. Since claim 5 depends from claim 1, claim 5 also should now be free of this rejection. Applicants reserve the right to prosecute the full scope of claim 1 prior to the present amendment in an appropriate continuing application.

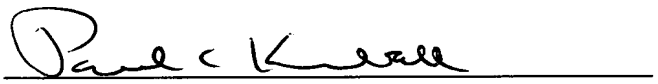
Applicants note that additional claim 28 expressly excludes species disclosed in Gubin, by way of the proviso that if either of R or R_1 is 2-methyl, the other is not 4-alkoxycarbonyl. Similarly, claim 28 expressly excludes species disclosed in the previously cited Litvinenko reference, by the proviso that if either R or R_1 is CH_3, the other is not H. Applicants therefore believe that claim 28 and its dependent claims also are free of the prior art.

All objections and rejections having been withdrawn or overcome by Applicants' arguments and the present amendment, Applicants therefore believe that the present case is in condition for allowance and respectfully request early notice to that effect.

If any issues remain to be addressed in this matter, which might be resolved by discussion, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number indicated below.

Respectfully submitted,

PIPER MARBURY RUDNICK & WOLFE LLP



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SERIAL NO. 09/118,388

DOCKET NO.: 9511-013-27

MARKED-UP COPY OF PARAGRAPHS, AS AMENDED

Replacement for last paragraph at page 5, lines 34-36 through page 6, lines 1-3 :

Preferred compounds of formula 1 include, for example, [1-phenacyl-2,3-dicarboxypyrdinium bromide] 1-phenacyl-2,3-dicarboxypyridinium bromide; [1-phenacyl-2,4-dicarboxypyrdinium bromide] 1-phenacyl-2,4-dicarboxypyridinium bromide ; [1-phenacyl-2,5-dicarboxypyrdinium bromide] 1-phenacyl-2,5-dicarboxypyridinium bromide; 1-phenacyl-3,5-dicarboxypyridinium bromide (AP5); [1-phenacyl-2,6-dicarboxypyrdinium bromide] 1-phenacyl-2,6-dicarboxypyridinium bromide ; [1-phenacyl-2,3-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,3-dicarboxyimidepyridinium bromide; [1-phenacyl-2,4-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,4-dicarboxyimidepyridinium bromide; [1-phenacyl-2,5-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,5-dicarboxyimidepyridinium bromide; and [1-phenacyl-2,6-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,6-dicarboxyimidepyridinium bromide.

Replacement for first full paragraph, page 35, lines 6-26 through page 36, lines 1-7:

In an alternative embodiment of the screening assay of Example 3, various concentrations of the test compound (*e.g.* 10-1000 μM) are incubated with the indicator cells in presence of a fixed concentration of 3-AP (*e.g.*, 200 μM). The toxicity of the test compounds may be evaluated in parallel cultures incubated without 3-AP; generally, the desired test compound will show cellular toxicity at much higher doses than those that confer protection against 3-AP (*e.g.*, 10-10,000-fold). The results of such tests are summarized in Table V, below:

Table V.

Effect of test compounds on 3-AP cytotoxicity

No effect or weakly protective	Toxic or no effect	Protective (50% Effective dose; 50% Toxic does)
Glial cell assay (HTB14)		
AP6 AP2 AP7 YA1 YA2 AP18 AP24 ascorbic acid 34P	AP9 AP12 AP19 AP20 AP23 AP28 3,5-di-tert.-butyl-4-hydroxytoluene	AP5 (150 μm; 7 mM) p27a (425 μM; 5 mM) AP21 (100 μM; not tested) AP22 (100 μM; 1 mM)

wherein:

AP6 is N-(2-phenyl-2-oxoethyl)-2-(2'-pyridine)-pyridinium bromide.

AP2 is N-(2-phenyl-2-oxoethyl)-quinolinium bromide.

AP7 is N-(2-phenyl-2-oxoethyl)-pyrazinium bromide.

YA1 is 2-phenyl-2-oxoethyl-dimethylphosphonate.

YA2 is N-(2-phenyl-2-oxoethyl)-triethylammonium bromide.

AP18 is N-(2-phenyl-2-oxoethyl)-4-tert.-butylpyridinium bromide.

AP24 is N-(2-phenyl-2-oxoethyl)-3-n-butylpyridinium bromide.

34P is pyridine-3,5-dicarboxylic acid.

AP9 is N-(2-phenyl-2-oxoethyl)-4-N,N-dimethylamino-pyridinium bromide.

AP12 is N-(2-phenyl-2-oxoethyl)-pyrazinium bromide.

AP19 is N-(2-phenyl-2-oxoethyl)-3-fluoropyridinium bromide.

AP20 is N-(2-phenyl-2-oxoethyl)-4-ethylpyridinium bromide.

AP23 is N-(2-phenyl-2-oxoethyl)-2,6-dihydroxymethylpyridinium bromide.

AP28 is N-(2-phenyl-2-oxoethyl)-3,5-diiodo-4-pyridinone.

AP5 is [N-(2-phenyl-2-oxoethyl)-2,5-dicarboxypyrdinium bromide] N-(2-phenyl-2-oxoethyl)-3,5-dicarboxypyridinium bromide; and this compound has also been coded PICVA-13.

AP21 is N-(2-phenyl-2-oxethyl)-3,4-dicarboxyamide-pyridinium bromide.

AP22 is N-(2-phenyl-2-oxoethyl)-3-bromo-5-carboxypyridinium bromide.

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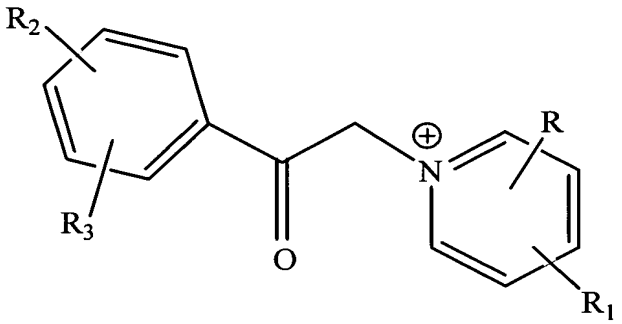
MARKED-UP COPY OF AMENDED CLAIMS

1. (Twice Amended) An ischemia-damage mitigating salt of a compound [or salt] having a formula I:



I

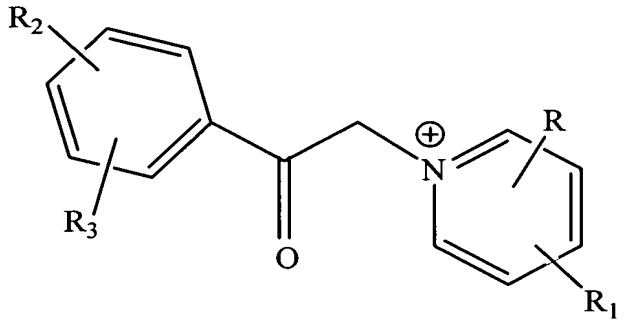
wherein R and R_1 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or branched C_{1-6} alkyl, straight or branched C_{2-6} alkenyl, straight or branched C_{1-6} alkoxy, a straight chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F), wherein [both R and R_1 cannot be hydrogen, and either] at least one of R or R_1 is COOH, wherein R_2 and R_3 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or branched C_{1-6} alkyl, straight or branched C_{2-6} alkenyl, straight or branched C_{1-6} alkoxy, a straight chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate or halide (Br, Cl, I, F), wherein R and R_1 are meta to each other and to the heteroatom.

5. (Amended) The ischemia-damage mitigating [compound] salt of claim 1 wherein R_2 and R_3 are both hydrogen.

6. (Amended) The ischemia-damage mitigating [compound] salt of claim 1 wherein R and R_1 are each COOH, and R_2 and R_3 are both hydrogen.

7. (Amended) The ischemia-damage mitigating [compound] salt of claim 1 wherein the compound is selected from the group consisting of [1-phenacyl-2,3-dicarboxypyrdinium bromide] 1-phenacyl-2,3-dicarboxypyridinium bromide; [1-phenacyl-2,4-dicarboxypyrdinium bromide] 1-phenacyl-2,4-dicarboxypyridinium bromide; [1-phenacyl-2,5-dicarboxypyrdinium bromide] 1-phenacyl-2,5-dicarboxypyridinium bromide; 1-phenacyl-3,5-dicarboxypyridinium bromide (AP5); [1-phenacyl-2,6-dicarboxypyrdinium bromide] 1-phenacyl-2,6-dicarboxypyridinium bromide; [1-phenacyl-2,3-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,3-dicarboxyimidepyridinium bromide; [1-phenacyl-2,4-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,4-dicarboxyimidepyridinium bromide; [1-phenacyl-2,5-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,5-dicarboxyimidepyridinium bromide; and [1-phenacyl-2,6-dicarboxyimidepyrdinium bromide]1-phenacyl-2,6-dicarboxyimidepyridinium bromide .

8. (Amended) A pharmaceutical composition comprising a salt of a compound from formula I in a pharmaceutically acceptable carrier, wherein formula I comprises:



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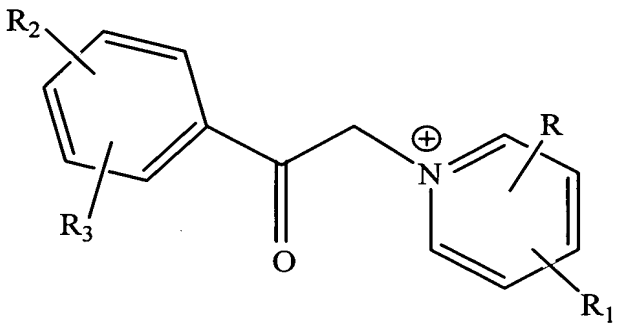
wherein R and R_1 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or branched C_{1-6} alkyl, straight or branched C_{2-6} alkenyl, straight or branched C_{1-6} alkoxy, a straight chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl,

COOH, nitrate, or halide (Br, Cl, I, F), wherein [both] at least one of R and R_1 [cannot be hydrogen] is COOH, wherein R_2 and R_3 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or branched C_{1-6} alkyl, straight or branched C_{2-6} alkenyl, straight or branched C_{1-6} alkoxy, a straight chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F).

14. (Amended) The pharmaceutical composition of claim 8 wherein the compound is selected from the group consisting of [1-phenacyl-2,3-dicarboxypyrdinium bromide] 1-phenacyl-2,3-dicarboxypyridinium bromide; [1-phenacyl-2,4-dicarboxypyrdinium bromide] 1-phenacyl-2,4-dicarboxypyridinium bromide; [1-phenacyl-2,5-dicarboxypyrdinium bromide] 1-phenacyl-2,5-dicarboxypyridinium bromide, 1-phenacyl-3,5-dicarboxypyridinium bromide (AP5); [1-phenacyl-2,6-dicarboxypyrdinium bromide] 1-phenacyl-2,6-dicarboxypyridinium bromide; [1-phenacyl-2,3-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,3-dicarboxyimidepyridinium bromide; [1-phenacyl-2,4-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,4-dicarboxyimidepyridinium bromide; [1-phenacyl-2,5-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,5-dicarboxyimidepyridinium bromide ; and [1-phenacyl-2,6-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,6-dicarboxyimidepyridinium bromide.

15. (Amended) A method for inhibiting tissue damage caused by ischemia, comprising administering an effective amount of a salt of a compound of formula I, wherein formula I comprises:



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wherein R and R_1 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or branched C_{1-6} alkyl, straight or branched C_{2-6} alkenyl, straight, or branched C_{1-6} alkoxy, a straight chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F), wherein [both] at least one of R and R_1 [cannot be hydrogen] is COOH, wherein R_2 and R_3 are independently hydrogen, sulfamide, carboxyamide, cyano, straight or branched C_{1-6} alkyl, straight or branched C_{2-6} alkenyl, straight or branched C_{1-6} alkoxy, a straight chain C_{1-6} alkyl or a straight chain C_{2-6} alkenyl having an ether link or an ester link, toluenyl, COOH, nitrate, or halide (Br, Cl, I, F).

21. (Amended) The method of claim 15 wherein the compound is selected from the group consisting of [1-phenacyl-2,3-dicarboxypyrdinium bromide] 1-phenacyl-2,3-dicarboxypyridinium bromide; [1-phenacyl-2,4-dicarboxypyrdinium bromide] 1-phenacyl-2,4-dicarboxypyridinium bromide; [1-phenacyl-2,5-dicarboxypyrdinium bromide] 1-phenacyl-2,5-dicarboxypyridinium bromide, 1-phenacyl-3,5-dicarboxypyridinium bromide (AP5); [1-phenacyl-2,6-dicarboxypyrdinium bromide] 1-phenacyl-2,6-dicarboxypyridinium bromide; [1-phenacyl-2,3-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,3-dicarboxyimidepyridinium bromide; [1-phenacyl-2,4-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,4-dicarboxyimidepyridinium

bromide; [1-phenacyl-2,5-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,5-dicarboxyimidepyridinium bromide; and [1-phenacyl-2,6-dicarboxyimidepyrdinium bromide] 1-phenacyl-2,6-dicarboxyimidepyridinium bromide.